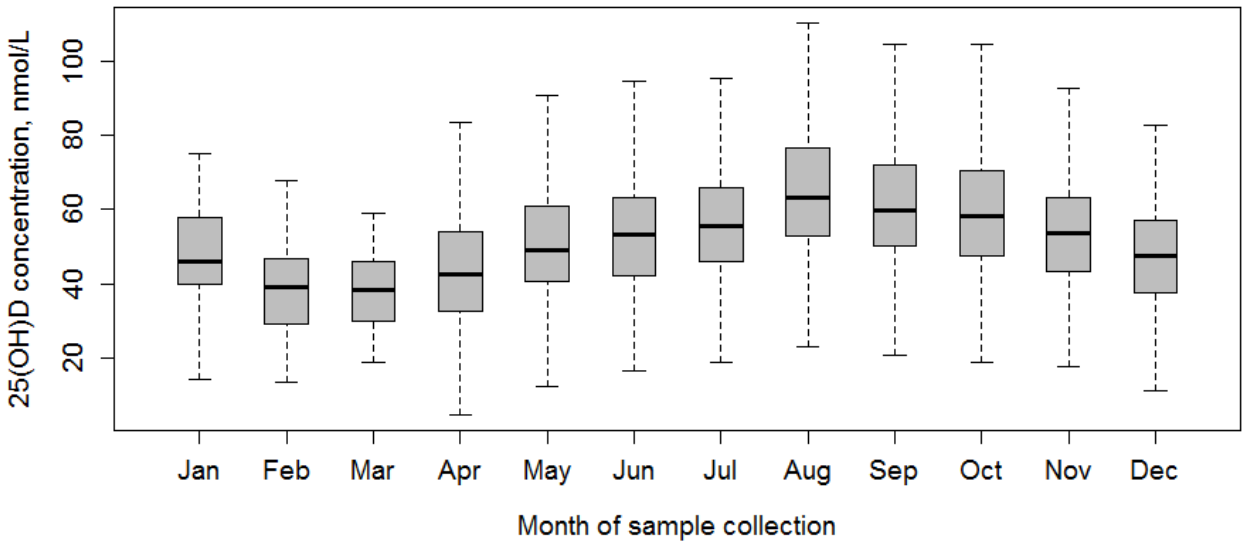
Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site-specific cancers in Japanese population: large case-cohort study within Japan Public Health Center-based Prospective Study cohort.

Supplementary figure A. Distribution of 25(OH)D concentration according to month of sample collection.



Supplementary methods.

To account for seasonal variability, we also applied an additional approach. We created standardized 25(OH)D values by using the residuals derived from a linear model in which the 25(OH)D concentration was regressed on age, gender and the two periodic functions of time t, $\sin(2\pi t/w)$ and $\cos(2\pi t/w)$, where t was expressed in years and a period of w=1 year was chosen because it is the most natural period for defining seasonal variations and has been used in previous studies investigating the effect of vitamin D (Munger *et al*, 2006). The standardized 25(OH)D values were then included in a Cox model to evaluate the association between 25(OH)D and cancer. The hazard ratios (95% confidence interval) per 25 nmol/L and 50 nmol/L increase in vitamin D concentration for total cancer was 0.92 (95% CI 0.84-1.00) and 0.84 (95% CI 0.71-1.00), respectively.

Supplementary table A. Classification of the main cancer types by ICD-0-3 code.

Cancer type	ICD-O-3	Number of cases
Colorectal	C18–C20	708
Gastric	C16	716
Liver	C22	178
Pancreatic	C25	138
Lungs	C34	463
Breast	C50	251
Prostate	C61	309
Biliary tract	C23, C24	124
Esophageal	C15	88
Leukemia	C42	94
Renal	C64–C66	71
Bladder	C67	73
Thyroid	C73	71
Lymph Node	C77	72
Uterine body	C54	53
Ovarian	C56	45
Other cancer	C00–C14, C17, C26, C30–C32, C37, C38, C41, C44, C47–C49, C51–C53, C55, C57, C60, C62, C70, C71, C74–C76, C80, C92	280
Total Cancer	C00–C97	3734

Supplementary table B. Median 25(OH)D and cut-off points (in parenthesis) for sex- and season-specific 25(OH)D quartiles among subcohorts.

	Quartile (Q) categories of plasma vitamin D (nmol/L)			
	Q1 (Low)	Q2 (Second)	Q3 (Third)	Q4 (High)
Men				
Winter	36.2 (<41.4)	47.4 (41.4-<53.4)	58.7 (53.4-<65.3)	74.1 (≥65.3)
Spring	37.7 (<43.4)	48.3 (43.4-<52.4)	58.7 (52.4-<64.4)	74.9 (≥64.4)
Summer	46.2 (<53.9)	58.4 (53.9-<62.9)	69.8 (62.9-<77.0)	87.9 (≥77.0)
Autumn	45.2 (<53.4)	58.4 (53.4-<63.9)	68.9 (63.9-<75.1)	85.0 (≥75.1)
Women				
Winter	28.2 (<34.2)	39.4 (34.2-<43.4)	48.2 (43.4-<53.2)	60.9 (≥53.2)
Spring	30.2 (<36.7)	41.2 (36.7-<44.9)	48.4 (44.9-<54.2)	61.4 (≥54.2)
Summer	36.2 (<42.2)	46.7 (42.2-<50.7)	54.9 (50.7-<60.2)	67.9 (≥60.2)
Autumn	37.2 (<43.2)	48.4 (43.2-<52.7)	56.9 (52.7-<61.7)	69.1 (≥61.7)

Winter (Dec-Feb), spring (Mar-May), summer (Jun-Aug), autumn (Sep-Nov).

Supplementary table C. Power calculation for the detection of an unadjusted effect of vitamin D exposure[a].

Number of cases	Effect size (Highest vs Lowest)	Power in Quartile Analysis	Power in Tertile Analysis
125	0.6	0.26	0.46
	0.7	0.17	0.28
	0.8	0.11	0.16
250	0.6	0.41	0.70
	0.7	0.25	0.45
	0.8	0.15	0.24
500	0.6	0.63	0.92
	0.7	0.40	0.68
	0.8	0.22	0.37
1000	0.6	0.87	0.99
	0.7	0.62	0.90
	0.8	0.33	0.58
2000	0.6	0.99	~1.00
	0.7	0.85	0.99
	0.8	0.51	0.80
3000	0.6	~1.00	~1.00
	0.7	0.94	~1.00
	0.8	0.64	0.91

[a]Power calculations for a two-sided type I error of 0.05, a full cohort size of 33,736 individuals, and a subcohort size of 4456 individuals (corresponding to a sampling fraction of around 0.132) based on Cai et al.(Cai & Zeng, 2004).

Supplementary table D. Hazard ratios (HRs) and 95% confidence intervals (CIs) of total and site-specific cancer* according to quartile categories of plasma vitamin D in men and women.

	Quartile (Q) categories of plasma vitamin D									
	Men					**Women**				
	Q1 (Low)	Q2 (Second)	Q3 (Third)	Q4 (High)	P_{trend}	Q1 (Low)	Q2 (Second)	Q3 (Third)	Q4 (High)	P_{trend}
All cancer										
No. of cases	410	443	420	457		430	349	375	417	
HR (95% CI)[a]	1 (Ref.)	0.87 (0.69 to 1.10)	0.73 (0.58 to 0.93)	0.76 (0.59 to 0.97)	0.01	1 (Ref.)	0.75 (0.63 to 0.90)	0.77 (0.64 to 0.93)	0.79 (0.65 to 0.95)	0.02
$P_{interaction}$					0.50					
Gastric cancer										
No. of cases	86	98	96	108		67	58	61	63	
HR (95% CI)[a]	1 (Ref.)	1.06 (0.74 to 1.51)	0.96 (0.67 to 1.39)	1.10 (0.76 to 1.58)	0.76	1 (Ref.)	0.86 (0.60 to 1.25)	0.90 (0.61 to 1.32)	0.87 (0.59 to 1.28)	0.54
$P_{interaction}$					0.59					
Colorectal cancer										
No. of cases	53	95	80	83		81	70	80	95	
HR (95% CI)[a]	1 (Ref.)	1.54 (1.03 to 2.28)	1.13 (0.74 to 1.73)	0.99 (0.64 to 1.53)	0.40	1 (Ref.)	0.78 (0.56 to 1.11)	0.84 (0.59 to 1.19)	0.89 (0.64 to 1.24)	0.64
$P_{interaction}$					0.06					
Liver cancer										
No. of cases	31	29	21	16		16	14	20	18	
HR (95% CI)[a]	1 (Ref.)	0.65 (0.36 to 1.20)	0.46 (0.24 to 0.89)	0.27 (0.12 to 0.61)	0.0009	1 (Ref.)	0.75 (0.34 to 1.61)	0.91 (0.44 to 1.91)	0.75 (0.35 to 1.63)	0.60
$P_{interaction}$					0.14					
Lung cancer										
No. of cases	68	59	51	69		41	28	37	43	
HR (95% CI)[a]	1 (Ref.)	0.62 (0.4 to 0.96)	0.44 (0.28 to 0.70)	0.61 (0.39 to 0.96)	0.02	1 (Ref.)	0.59 (0.36 to 0.98)	0.74 (0.45 to 1.22)	0.80 (0.49 to 1.32)	0.60
$P_{interaction}$					0.50					

*Site-specific cancers with case numbers of ≥130.

[a]Adjusted for age, body mass index, smoking, alcohol use, physical activity, family history of cancer, and reported diabetes history.

Supplementary table E. Hazard ratios (HRs) and 95% confidence intervals (CIs) of site-specific cancer* according to tertile categories of plasma vitamin D in men and women.

	Tertile (T) categories of plasma vitamin D							
	Men				**Women**			
	T1 (Low)	T2 (Middle)	T3 (High)	P_{trend}	T1 (Low)	T2 (Middle)	T3 (High)	P_{trend}
Esophageal cancer								
No. of cases	24	10	27		4	4	3	
HR (95% CI)[a]	1 (Ref.)	0.32 (0.14 to 0.72)	0.93 (0.44 to 1.96)	0.92	1 (Ref.)	1.08 (0.28 to 4.13)	1.00 (0.24 to 4.20)	0.99
$P_{interaction}$				0.19				
Biliary tract cancer								
No. of cases	17	14	15		24	19	26	
HR (95% CI)[a]	1 (Ref.)	0.68 (0.33 to 1.40)	0.53 (0.25 to 1.13)	0.10	1 (Ref.)	0.62 (0.34 to 1.15)	0.72 (0.38 to 1.36)	0.35
$P_{interaction}$				0.74				
Pancreatic cancer								
No. of cases	20	14	15		22	22	21	
HR (95% CI)[a]	1 (Ref.)	0.61 (0.29 to 1.28)	0.67 (0.29 to 1.53)	0.33	1 (Ref.)	0.97 (0.52 to 1.80)	0.89 (0.46 to 1.73)	0.74
$P_{interaction}$				0.55				
Leukemia								
No. of cases	10	17	16		11	21	12	
HR (95% CI)[a]	1 (Ref.)	1.33 (0.54 to 3.26)	1.09 (0.40 to 2.94)	0.91	1 (Ref.)	1.73 (0.81 to 3.7)	0.93 (0.38 to 2.29)	0.82
$P_{interaction}$				0.68				
Kidney cancer								
No. of cases	11	16	13		9	7	9	
HR (95% CI)[a]	1 (Ref.)	1.26 (0.56 to 2.82)	1.09 (0.51 to 2.34)	0.84	1 (Ref.)	0.65 (0.22 to 1.92)	0.59 (0.20 to 1.79)	0.37
$P_{interaction}$				0.69				
Bladder cancer								
No. of cases	10	21	12		6	6	5	
HR (95% CI)[a]	1 (Ref.)	1.60 (0.69 to 3.75)	0.92 (0.35 to 2.41)	0.79	1 (Ref.)	0.94 (0.31 to 2.89)	0.70 (0.23 to 2.12)	0.53
$P_{interaction}$				0.66				
Lymphoma								
No. of cases	15	14	8		15	10	19	
HR (95% CI)[a]	1 (Ref.)	0.70 (0.30 to 1.62)	0.38 (0.12 to 1.17)	0.09	1 (Ref.)	0.51 (0.21 to 1.21)	0.80 (0.36 to 1.78)	0.70
$P_{interaction}$				0.14				
Thyroid cancer								
No. of cases	2	4	2		22	17	21	
HR (95% CI)[a]	1 (Ref.)	2.16 (0.41 to 11.40)	1.56 (0.16 to 15.42)	0.63	1 (Ref.)	0.89 (0.45 to 1.79)	1.22 (0.59 to 2.51)	0.62
$P_{interaction}$				0.53				

*Site-specific cancers with case numbers of <130.

[a]Adjusted for age, body mass index, smoking, alcohol use, physical activity, family history of cancer, and reported diabetes history.

References.

Cai J, Zeng D (2004) Sample size/power calculation for case-cohort studies. *Biometrics* **60**(4)**:** 1015-24

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